Bayer HealthCare
Consumer Care Division

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Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane
Room 1061 (HFA-305)
Rockville, Maryland 20852

Catherine W. Fish, MS, RD
Senior Associate Director
Regulatory Affairs

Re: Docket 77N-0094

Submission of Database from Primary Prevention Studies Supporting Aspirin Primary Prevention Professional Labeling

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Dear Drs. Stockbridge and Ellenberg:

Reference is made to Bayer HealthCare's Citizen Petition submitted February 11, 2003, which consisted of published information supporting the use of aspirin for treatment of the primary prevention of myocardial infarction (MI) in those with a 10 year risk of 10% or greater, and to the Supplement document submitted September 9, 2004, which consisted of additional information to support the original Citizen Petition.

Since the Citizen Petition submission, the subject of the labeling of aspirin for the primary prevention of myocardial infarction has been the focus of a December 8, 2003 Cardiovascular and Renal Drugs Advisory Committee hearing, as well as face-to-face meetings, and numerous telephone contacts with FDA. In addition, the overwhelming support for the use of aspirin by broader at-risk patients from the major professional and scientific organizations involved in cardiovascular risk management has continued during the FDA's review of the Petition. As such, it is evident that there is continued interest by all parties in the public health importance of the approval of this indication for aspirin.

Bayer HealthCare has worked diligently to facilitate the transfer of the original data from the Primary Prevention trials to allow the Agency to undertake its own evaluation of the benefits and risks of aspirin in the proposed indication – the use of aspirin in individuals at moderate risk or greater of coronary heart disease (CHD), who have not experienced a previous MI. We have been working with a third party group to facilitate the submission of the information requested. Since data from all five Primary

Prevention studies were supplied to complete the ATT Primary Prevention Subgroup analysis, Dr. Colin Baigent of Oxford's Clinical Trials Study Unit (CTSU), is serving as the coordinating center for the transfer of these data. In addition, each of the investigators has agreed to collaborate with Dr. Baigent in responding to any queries or analysis requests the Agency may have.

In light of the concerns associated with the FDA's previous review of the data, as presented at the December 8, 2003 Cardiovascular and Renal Drugs Advisory Committee and discussed at the April 30, 2004 meeting with the Agency, we urge the Medical Reviewers and Statistical Reviewers to collaborate with each of the Principal Investigators. We believe that a collaborative effort is necessary to establish appropriate endpoints, methods for the handling of silent MI, as well as other issues that have been discussed with the Agency.

We herewith present the following points that should be considered in the review of the Primary Prevention database and provide perspective relevant to the benefits and risks of aspirin in the proposed indication:

- Bayer HealthCare's action requested specifically seeks approval for the use of aspirin in individuals at moderate risk or greater of coronary heart disease (CHD), who have not experienced a previous MI.

- There is clear evidence from five adequate and well-controlled clinical trials, involving over 55,000 apparently healthy subjects, demonstrating the benefits of low dose aspirin (75-325 mg) in reducing the risk of MI (32%). Specific evaluation of the subset of moderate risk patients confirms a reduced risk of non-fatal MI of 35%.

- While the patients' average risk level in four of the five Primary Prevention studies was deemed to be low, all five studies included patients at various levels of risk. The Thrombosis Prevention Trial, based on its specific goal of enrolling moderate risk patients, is of particular importance in the evaluation of the proposed indication. We urge the Agency to expedite the review of this very important study to support the labeled indication to reduce the risk of a first MI in patients at moderate CHD risk, defined as a 10 year risk of coronary heart disease that exceeds 10%.

- We seek common ground with respect to the wording of an indication that is supported by the available evidence in patients at moderate or greater risk of CHD and achieves the desired mutual objective of ensuring appropriate aspirin use in patients at significant risk of MI. Conservative labeling has been proposed to enhance the benefit-to-risk relationship by restricting the use of aspirin to individuals whose 10-year risk exceeds 10% (moderate risk), in spite of evidence of effectiveness in reducing the risk of MI in even low risk patients in the five primary prevention studies (as well as in moderate and high risk individuals).

- The long-term safety of aspirin in the management of cardiovascular disease is well studied (over 200 studies involving more than 200,000 individuals). The adverse event profile is reflected in the current labeling of the approved indications of aspirin and would be the same for the proposed indication.

- Major professional scientific and medical bodies, including the American College of Cardiology, American Diabetes Association, The American Heart Association, the US Preventive Services Task Force, and many others, support the use of aspirin in individuals of at least moderate risk (greater than 10% 10-year risk) of CHD.

Bayer urges the Agency to evaluate the CTSU submission expeditiously. We remain committed to helping the Agency with regard to their evaluation of all the supporting information under review and to helping ensure that the Agency has access to the latest available data. The healthcare community and general population as a whole are interested in greater clarity regarding appropriate aspirin use and we continue to believe that our efforts together in this regard can have significant public health impact.

Thank you very much for your continued interest in this Petition. Should you have any questions, please feel free to contact me at 973-254-4793.

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Submitted in duplicate